REMARKS

The Office Action

Claims 1-8, 11, 13-20, 23, 25-32, 35, 37-44, 47, 49-56, 59 and 61-110 are pending. Claims 11, 23, 35, 47, 59, 61-72, 74, 76, 78, 80-82, 84, 86, 88, 90-92, 94, 96, 98, 100-102, 104, 106, 108 and 110 are under examination in this application. Claims 1-8, 13-20, 25-32, 37-44, 49-56, 73, 75, 77, 79, 83, 85, 87, 89, 93, 95, 97, 99, 103, 105, 107 and 109 are withdrawn as being drawn to an unelected group.

Applicants note that in the Supplemental Restriction Requirement mailed in this case on 27 June 2007, claims 98 and 108 were listed as patentably distinct species under both Species A and Species B. Applicants believe that claims 98 and 108 belong with their corresponding claims (e.g., see claims 68, 78 and 88) under Species A and that claims 99 and 109 (which were not mentioned in the Supplemental Restriction Requirement) belong with their corresponding claims (e.g., see claims 69, 79 and 89) under Species B. In Applicants' Response to Office Action, dated 22 August 2007, Applicants responded to the Supplemental Restriction Requirement by electing Species A, embodied by claims 63-66, 68, 73-76, 78, 83-86, 88, 93-96, 98, 103-106 and 108. Therefore, Applicants submit that claims 98 and 108 are pending in the present application. Accordingly, Applicants have listed claims 99 and 109 as "withdrawn" in the above claims listing.

Claims 11, 23, 35, 47, 59, 61, 62, 64, 66, 68, 70, 71, 72, 74, 76, 78, 80-82, 84, 86, 88, 90-92, 94, 96, 99-102, 104, 106, 109 and 110 stand rejected under 35 USC § 112, first and second paragraphs. Claims 11, 23, 35, 47, 61, 62, 64, 66, 68, 70, 71, 72, 74, 76, 78, 80-82, 84, 86, 88, 90, 101, 102, 104, 106, 109 and 110 stand rejected under 35 USC § 101.

Claim Amendments

Applicants have amended claims 61, 71, 81, 91, 101, 102, 104, 106, 108 and 110 herein. Support for the amendments is found in throughout the specification, and in the claims as originally filed. Amendments to the claims are made to more clearly describe the subject matter that Applicants believe is patentable. Applicants

respectfully submit that the claims were sufficiently described in their prior form, and enter the amendments without prejudice, in the interest of expediting allowance of the claims, and in order to address concerns stated by the Examiner with respect to 35 U.S.C. §§ 112 and 101. No new matter is added by the amendments.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph

At paragraph 4 of the detailed action, the Examiner has rejected claims 11, 23, 35, 47, 59, 61, 62, 64, 66, 68, 70, 71, 72, 74, 76, 78, 80-82, 84, 86, 88, 90-92, 94, 96, 99-102, 104, 106, 109 and 110 under 35 USC § 112, first paragraph, as failing to comply with the enablement requirement. In particular, the Examiner states that the claims contain subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner sets forth the *In re Wands* factors to be considered in determining whether a disclosure would require undue experimentation. As a preliminary issue, Applicant notes that the Examiner appears to focus on two terms: "retention time transformation function" and "transformed retention time tolerance" in his analysis of several of the *In re Wands* factors. As discussed in further detail below, Applicants have removed the term "transformed retention time tolerance" from the claims. Prior to analyzing the *In re Wands* factors, Applicants provide the following comments on the enablement of the term "retention time transformation function".

Regarding the enablement of "retention time transformation function", the Examiner states, "although the specification does mention performing a transformation of the peptide map based on the retention time at pages 27-30, the specification does not teach one of skill in the art how to derive a retention time. ... Given that the specification does not provide examples or guidance on how to derive a retention time transformation function, one of skill in the art would have to perform undue experimentation in order to determine the retention time transformation function needed to align different peptide maps."

Applicants submit that one skilled in the art, upon reading the specification can derive a retention time transformation function without undue experimentation. The method for derivation of a retention time transformation function is described and illustrated in the specification using standard algorithmic terminology. In particular, at page 28, lines 9-14 of the specification, the algorithm is described as having five steps:

> "...the process of peptide map alignment can be described as five steps: determining peptide neighbors, retention time clustering, best adjustment, iteration and optimization, and application of adjustment."

These five steps are described in detail in the specification at page 28, line 22 to page 30, line 7, respectively.

Furthermore, at page 28, lines 15-16 the specification states: "Figure 13 is a flowchart detailing the components of a Peptide Map Alignment Module (PAMAM)". Figure 13 displays the five steps of the algorithm using the traditional algorithm flowchart style of boxes for processing steps, diamonds for decision steps and arrows to indicate flow from step to step. Therefore, Figure 13 can be used by one skilled in the art to further understand the five steps in the algorithm.

Applicants submit that each of the five steps of the algorithm are sufficiently defined such that one skilled in the art can reproduce them without undue experimentation. Each step is addressed in further detail below.

Step 1: Determining Peptide Neighbors

The first step in the algorithm is to determine peptide neighbors. This step is described in the specification at page 28, line 29 to page 29, line 6. The rule for determining peptide neighbors between peptide maps A and B (as described, for example, at page 28, line 30 to page 29, line 1) is set forth as follows:

> "for each peptide p in A, define the neighbors of p in B to be all peptides in B of the same charge as p and within a predefined mass and retention time window of p."

Upon reading the above instructions, one skilled in the art knows to define the neighbors of p in B to be all peptides in B that fall within a certain tolerance based on the mass and retention time (rt) window of p. Such matching tolerances are explicitly defined at page 29, lines 2-5 as well:

> "The m/z matching tolerance is typically very precise (less than 0.10 Da)...The rt matching tolerance is defined loosely depending on the application of the alignment but is typically less than 8 minutes."

These tolerances are specified explicitly, and therefore, it would not require undue experimentation to obtain them and apply them to determine the peptide neighbors for each peptide p in A.

Step 2: Retention Time Clustering

The second step of the algorithm is that of retention time clustering, and is described in the specification at page 29, lines 8-15. The rule for determining retention time clusters is set out at page 29, lines 10-11 and involves first:

> "sorting peptides in p from low to high retention time".

Applicants submit that this step can readily be carried out by one skilled in the art. In support of this assertion, Applicants direct the Examiner to the Declaration of Paul Kearney Under 37 C.F.R. § 1.132 (the "Declaration"). At paragraph 4 of the Declaration, Dr. Kearney states that sorting is a standard algorithm available even in commercial software such as Microsoft Excel. Dr. Kearney also states that sorting is one of the first algorithmic procedures taught to undergraduate students in computer science courses. The Declaration also provides a section of an undergraduate textbook on sorting (see Exhibit A) to demonstrate that sorting is taught at the undergraduate level of computer science courses.

The next step in performing retention time clustering is described at page 29, lines 11-12 and involves:

"grouping peptides into clusters of peptides of similar retention time (i.e. within a predefined difference). These groupings are called retention time clusters."

Applicants submit that the grouping of peptides by similar retention time can be achieved by one skilled in the art without undue experimentation. In support of Applicants' contention, Applicants direct the Examiner to the Declaration of Dr. Kearney. At paragraph 5 of the Declaration, Dr. Kearney states that the grouping of peptides by similar retention time can be achieved by those in the computer science field using any one of a number of standard procedures such as hierarchical clustering, k-means clustering, multidimensional scaling or simple histogram analysis. The Declaration also states that grouping of peptides along the retention time dimension is an instance of a generic problem of clustering objects along some dimension (in this instance, it is retention time). The Declaration further states that clustering is a well-known procedure in the computer science field; and provides examples of an article on the subject (see Exhibit B) as well as an excerpt from a textbook (see Exhibit C).

The next step in performing retention time clustering is determining the "column offset". As provided at page 29, lines 14-15 of the specification, the procedure for this step is:

"the distribution mode is used to define the column offset but any measure of centrality can be used."

Applicants submit that the mode of a distribution can be applied by one skilled in the art without undue experimentation. In support of this assertion, Applicants direct the Examiner to the Declaration of Dr. Kearney. As stated at paragraph 6 of the Declaration, the mode of a distribution, and more generally, measures of centrality such as median and mean, are well-defined concepts found in any introductory statistics textbook and are easily applied by someone working in the area of computer science. The Declaration also provides an example of a textbook that teaches how a mode of a distribution can be applied (see Exhibit D).

In light of the above comments and the Declaration of Dr. Kearney, Applicants submit that one skilled in the art could perform retention time clustering, by sorting the peptides from low to high retention time, grouping the peptide into retention time clusters and determining the column offset, as each of these steps can be performed by one skilled in the art without undue experimentation.

Step 3: Best Adjustment

The third step of the algorithm is determining the best adjustment. This step is described at page 29, lines 17-25 of the specification. The rule for determining the best adjustment is clearly set forth at page 29, lines 18-21:

> "For each retention time cluster, the optimum retention time adjustment
> is determined. The constraint is that all peptides within the cluster can
> only be matched to one of its peptide neighbors in B and that the
> retention time adjustment is shared by all of the peptides within the
> cluster."

Lines 21-22 of page 29 describe how the optimum retention time adjustment can be algorithmically determined for each retention time cluster:

> "Algorithmically, the optimum retention time adjustment can be
> determined by many approaches including integer programming."

Applicants submit that integer programming is offered as an alternative method to the one described in more detail in the specification (which is discussed below in further detail). Applicants further assert that integer programming can be performed by one skilled in the art with out undue experimentation. In support of Applicant's contention, the Examiner is directed to paragraph 7 of the Declaration of Dr. Kearney in which it is stated that integer programming is a standard algorithmic concept known to those practicing in the area of computer science. The Declaration also states that integer programming is taught in many standard textbooks, and provides an excerpt from such a textbook as Exhibit E.

Page 29, lines 22-25 also describes a specific approach to finding the optimum retention time adjustment:

"matched peptides within +/- 2 minutes (or some other empirically determined value) of the column offset are kept for further analysis. A median smoothing window is applied along retention time to obtain local retention time offset values. This results in the blue line depicted in FIG. 17."

The "matched peptides" and "column offset" concepts have been described above. Finding those peptides within +/- 2 minutes of the column offset is then clear and can be accomplished by one skilled in the art. For each retention time cluster, a "median smoothing window" is applied to obtain local retention time offset values. Applicants submit that one skilled in the art can apply a median smoothing window to the retention cluster. In support of Applicant's assertion, the Examiner is directed to paragraph 8 of the Declaration of Dr. Kearney. The Declaration states that median smoothing window is a concept taught in introductory signal processing and statistics courses. The Declaration also provides Exhibit F as an example of a textbook that teaches this concept.

Applicants also submit that this step of the algorithm is described in Figure 17 and at page 16, lines 7-12, which describes Figure 17:

"FIG. 17. Retention Time Transformation Function. An example of the dynamic offset routine allows for the matching of peptides in two different LC-MS spectra, independent of the variability introduced by different pumps, different columns, or pump rate fluctuation. The blue line is the learned retention time correction function required for matching peptides."

The above description clearly states that Figure 17 is an example of a Retention Time Transformation Function.

Based on the above comments and the Declaration of Dr. Kearney, Applicants submit that one skilled in the art, upon reading the specification, could determine the best adjustment, as each of the methods for performing this step are known to the skilled person.

Step 4: Repeat and Optimizing

The fourth step of the algorithm is described at page 29, lines 27-30. This step involves simply iterating steps (2) and (3), as described above, to optimize the retention time adjustment (i.e., the retention time transformation function) for different choices of the retention time clusters. Iterating to improve a solution is a standard algorithmic technique, however, the criterion to determine the optimal solution must be defined. The criterion for the purposes of this invention is set out at page 29, lines 28-29:

"An optimal solution is one that minimizes the retention time adjustment over all retention time clusters."

Therefore, one skilled in the art repeats steps (2) and (3), as described above, with the goal being to minimize the retention time adjustment over all retention time clusters. Since steps (2) and (3) can be performed by one skilled in the art without undue experimentation, Applicants contend that one skilled in the art can reiterate these steps to carry out step (4) of the algorithm.

Step 5: Apply Adjustment

The fifth and final step of the algorithm is applying the optimal retention time adjustment (as determined in step (4)) to all retention clusters. This step is clearly described at page 30, line 2, where it states :

"The optimal retention time adjustment is applied to all retention time clusters."

The method for performing this step is set out at page 30, lines 1-7 of the specification. Applicants submit that both the "optimal retention time adjustment" and

"retention time clusters" are as described above in the fourth and second steps, respectively. Since both of these terms have been described, one skilled in the art could apply the optimal retention time adjustment to all retention time clusters without undue experimentation.

Matched peptides are determined as described at page 30, lines 2-5:

"If a peptide is within a predefined retention time threshold of one of its neighbors then they are matched. Typically, matched peptides within +/- 0.5 minutes (or some other empirically determined value) of the median smoothed function are selected as the final matched peptides."

Applicants submit that the above statements clearly set out the criterion for a peptide to be matched to one of its neighbors. The median smoothed function has been described in the third step of the algorithm. Finally, a recommended tolerance is given (0.5 minutes) so that one skilled in the art would not need to perform excessive experimentation to implement this step of the algorithm.

Applicants also point out that Figure 17 provides a concrete example of a retention time transformation function.

Applicants submit that in view of the specification, the above comments and the Declaration of Dr. Kearney, the retention time transformation function can be derived by those skilled in the art without undue experimentation.

In re Wands Analysis

Having provided the above comments on the enablement of the term "retention time transformation function", Applicants now address the *In re Wands* factors for determining whether a disclosure would require undue experimentation. The test for enablement is whether a person of ordinary skill in the art can make and use the claimed invention without undue experimentation. *In re Wands*, 858 F. 2d731, 737 USPQ 2d 1400, 1404 (Fed. Cir. 1988). Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of

experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. These factors are addressed below.

<u>Nature of the Invention</u>

The claimed invention, as evidenced by claim 61, which, as amended herein, is for purposes of response to this rejection representative, comprises methods for matching a plurality of biomolecules between two or more biological samples, comprising:

a)   obtaining mass-to-charge ratio data, chromatographic retention time data and ion intensity data corresponding to biomolecules of two or more biological samples that have been separated and detected by liquid chromatography coupled with mass spectrometry;

b)   generating peptide maps from the data corresponding to the biological samples, the peptide maps comprising mass-to-charge ratio (m/z) co-ordinates ion intensity coordinates, and chromatography retention time co-ordinates;

c)   deriving a retention time transformation function that corrects for differences in chromatographic retention time between the peptide maps;

d)   applying the derived retention time transformation function to the peptide maps to align the peptide maps thereby matching a plurality of biomolecules between two or more biological samples; and

e)   outputting the aligned peptide maps to a user.

The Examiner states that the invention appears to require computational methods to transform a peptide map. Applicants submit that the nature of the invention is such that a retention time transformation, as discussed in detail above, must be derived and applied to the peptide maps in order to align them.

<u>Relative Skill of Those in the Art</u>

The Examiner states that the skill is high. Applicants agree that the level of skill in the art is high. Many practitioners in this area hold Ph.D. degrees and a number of them have significant post-doctoral experience. As discussed above and in the Declaration of Dr. Kearney, a person of skill in the art would have learned each step for deriving a retention time transformation function as part of becoming a person of skill in the area of using mass spectrometric techniques to assess biological samples.

<u>State of the Prior Art</u>

The Examiner states that the prior art does not appear to teach transforming peptide maps using retention times. As discussed above and in the Declaration of Dr. Kearney, the various steps for deriving a retention transformation function are set out at page 28, line 1 to page 30, line 7 of the specification. These steps are well known in the art, with many of them being taught at the undergraduate level. Applicants submit that it is not necessary that the prior art teach the entire method. What is required is that the specification teach one skilled in the art how to derive the retention time transformation function without undue experimentation. By setting out the steps for deriving a retention time transformation function, each of which, as discussed above and in the Declaration of Dr. Kearney, is known in the art, the specification is enabling for a method for deriving a retention time transformation function.

<u>Amount of Guidance Provided in the Specification</u>

The Examiner states that the specification does mention that an algorithm is used to transform the peptide maps on pages 27-30, however it does not teach the equations or methods used to perform the transformation. As discussed in great detail above and in the Declaration of Dr. Kearney, the specification provides sufficient guidance such that one skilled in the art can derive a retention time transformation function without undue experimentation.

Number of Working Examples

The Examiner states that there are no working examples. Applicants first note that compliance with the enablement requirement does not turn on whether an example is disclosed. That being said, Applicants submit that many of the drawings filed with the application and their corresponding descriptions as set forth in the "Brief Description of the Drawings" section of the specification depict and describe working examples. For example, Figure 18 shows an alignment of a map from LC-MS with a map from LC-MS-MS (see page 16, lines 13-16). And Figure 16 shows peptide map A aligned with peptide map B (see page 16, lines 3-6). Applicants submit that in order to get to the final step of aligning peptide maps, as recited in step (d) of claim 61, for example, Applicants had to perform steps (a), (b) and (c). Figure 17 depicts the predicted column offset and the retention time transformation function for a pair of injections (see page 27 lines 28-29 and page 16, lines 7-12). Furthermore, Figure 9 shows the generation of a peptide map, as recited in step (b) of claim 61. Applicants submit that in order to generate the peptide maps, step (a) of claim 61 had to be performed.

Quantity of Experimentation Necessary

The Examiner states that a great deal of experimentation would be required to determine how to transform the peptide maps based on retention time or what is a transformed retention time tolerance. Applicants submit that it would not require undue experimentation to transform the peptide maps by applying the derived retention time transformation function to peptide maps as discussed above.

Predictability of the Art

The Examiner states that the biological sciences are considered an unpredictable art. It is not clear to the Applicant what part of Applicants' invention the Examiner considers to be unpredictable due to the unpredictability of the biosciences. Applicants submit that although the samples being assessed are biological materials, the use of mass spectrometric techniques to assess peptides is a predictable art. One skilled in the art could, by following the directions set out in the specification

predictably match a plurality of biomolecules between two or more samples by using the predictable mass spectrometric techniques described herein.

Breadth of the Claims

The Examiner states that the claims include the step of deriving a retention time transformation function. It appears that the Examiner considers the claims to be too broad because of this step. Applicants submit that, as discussed above, the step of deriving a retention time transformation function is i) described in the specification; and ii) is able to be derived by a person of skill in the art. Therefore, the claims are not overly broad.

Based on the above comments, Applicants submit that the specification provides sufficient guidance for methods of matching a plurality of biomolecules between two or more biological samples, as recited in the rejected claims. Although the above comments specifically address the enablement of claim 61, the Examiner's concerns with claim 61 apply equally to claims 11, 23, 35, 47, 59, 62, 64, 66, 68, 70, 71, 72, 74, 76, 78, 80-82, 84, 86, 88, 90-92, 94, 96, 99-102, 104, 106, 109 and 110. Accordingly, Applicants submit that the arguments provided above apply equally to all of the rejected claims. Applicants respectfully request that the rejection of claims 11, 23, 35, 47, 59, 61, 62, 64, 66, 68, 70, 71, 72, 74, 76, 78, 80-82, 84, 86, 88, 90-92, 94, 96, 99-102, 104, 106, 109 and 110 under 35 USC § 112, first paragraph be withdrawn.

Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

At paragraph 6 of the detailed action, the Examiner has rejected Claims 11, 23, 35, 47, 59, 61, 62, 64, 66, 68, 70, 71, 72, 74, 76, 78, 80-82, 84, 86, 88, 90-92, 94, 96, 99-102, 104, 106, 109 and 110 stand rejected under 35 USC § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. In particular, the Examiner states that claims 61, 71, 81, 91 and 101 each recite obtaining ion intensity data, but that data is never used in the claims. Therefore, according to the Examiner, it is unclear as to what role ion intensity data fulfills in the instant claims. Applicants have amended each of claims 61, 71, 81, 91 and 101 such that in step (b) of each of the claims the

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use of the ion intensity data is now recited. Support for the amendment of claims 61, 71, 81, 91 and 101 is found throughout the specification, for example, at page 24, line 21 to page 25, line 14. In view of these claim amendments Applicants respectfully request that this portion of the rejection be withdrawn.

The Examiner also states that claims 61, 71, 81, 91 and 101 each recite "transformed retention time tolerance" in step (e) of each of these claims, but that it is unclear what the term means. Applicants note that the term "transformed retention time tolerance" has been removed from each of claims 61, 71, 81, 91 and 101 in order to provide additional clarity to each of these claims. The removal of the term from the claims is not an admission by the Applicants that the term is indefinite. In view of the claim amendments, this portion of the rejection may be withdrawn.

The Examiner also states that claims 102, 104, 106, 109 (interpreted by Applicants, as discussed above, to mean claim 108), and 110 recite the limitation "the computer readable memory", but that there is insufficient antecedent basis for this term in the claims. Each of claims 102, 104, 106, 108 and 110 have been amended herein such that they recite the stored computer useable <u>media</u> as recited in claim 101, from which each of these claims, directly or indirectly depends.

Applicants respectfully submit that in light of the claim amendments and the above comments, the rejections under 35 USC § 112, second paragraph may be withdrawn.

Claim Rejections Under 35 U.S.C. § 101

At paragraph 8 of the detailed action, the Examiner has rejected claims 11, 23, 35, 47, 59, 61, 62, 64, 66, 68, 70, 71, 72, 74, 76, 78, 80-82, 84, 86, 88, 90, 101, 102, 104, 106, 109 and 110 under 35 USC § 101 as being directed to non-statutory subject matter. In particular, the Examiner states that the instant claims are drawn to a process involving the judicial exception of a computational algorithm. The Examiner points out that claims drawn to a judicial exception are non-statutory unless the claims include a practical application of that judicial exception as evidenced by a physical transformation of the claimed invention, or if the claimed invention produces a useful,

tangible and concrete final result. The Examiner asserts that in the instant claims there is no physical transformation by the claimed invention, and thus the Examiner must determine if the instant claims produce a useful, tangible, and concrete final result. The Examiner then concludes that since there is no final result in the claims, the claims do not include a useful, concrete and tangible final result. The Examiner also notes that this rejection could be overcome by amendment of the claims to recite that a result of the method is outputted to a user.

Applicants note that claims 61, 71, 81, 91 and 101 have been amended herein. In particular, claim 61 has been amended herein to incorporate the Examiner's suggestion of outputting the results to a user. In view of the claim amendments, Applicants submit that the utility requirements have been met. Withdrawal of the rejections is respectfully requested.

CONCLUSION

Applicant believes that it has fully responded to the Examiner's concerns, and that the application is in condition for immediate allowance. Applicant respectfully requests reconsideration and immediate allowance of the claims
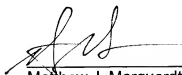
Applicants also point out that Applicants' reference number for the present application has changed from 33766-2037 to 34806-2003. Applicants kindly request that reference number 34806-2003 be used in all future communications.

Please charge any deficiency or credit any overpayment in any fee required for this response, including any required petition fee not already submitted, to Deposit Account No. 50-2651.

Applicant requests that any questions concerning this matter be directed to the undersigned at (416) 865-8242.

Respectfully submitted,

Dated: 30 APRIL 2008

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